

APPLICANTS: Ward et al.  
SERIAL NO: 10/719,370

DOCKET NO: PTS-0070US.P1 (ISIS.038CP1)

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Docket No.: PTS-0070US.P1 (ISIS.038CP1) Customer No.: 55389  
Applicants: Ward et al. Confirmation No.: 3593  
Serial No.: 10/719,370 Group Art Unit: 1635  
Filed: November 21, 2003 Examiner: Zara, Jane J.  
Title: MODULATION OF HIF1 $\alpha$  AND HIF2 $\alpha$  EXPRESSION

MS Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Examiner:

## DECLARATION PURSUANT TO 37 C.F.R. § 1.131

I, Eric G. Marcusson, residing at 260 King Street #727, San Francisco, CA 94107, a citizen of the United States of America, do declare and state that:

1. I am an inventor of the subject matter claimed in the above-identified application.
2. I have reviewed the specification and claims as filed as well as the amended claims and new claims appearing in the response submitted herewith.
3. I have reviewed the Office Action mailed June 27, 2006. I understand the Examiner rejected claims 1, 3-8, 22-25, 33, 37 and 44 under 35 U.S.C. § 102(e) as being anticipated by Usman *et al.* (WO 2005/035759).
4. This declaration is being submitted to establish that the subject matter described and currently claimed in the above-referenced patent application was conceived by me and reduced to practice in the United States prior to August 20, 2003, which is the earliest date to which the Usman *et al.* reference claims priority. In support of this conception and reduction to practice, a copy of a page from my laboratory notebook is provided herewith as Exhibit A. Dates and information not related to the completion of the claimed invention have been redacted. The

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table has been labeled "Table 1" for the purpose of clarity in this declaration; however, in my original notebook page this table is unlabeled.


a. As evidenced in Exhibit A, I designed a series of oligonucleotides to identify sequences that cross-react with HIF1 $\alpha$  and HIF2 $\alpha$ . The human HIF1 $\alpha$  and HIF2 $\alpha$  nucleotide sequences were compared to identify regions of identity. Based on this information, antisense oligonucleotides were designed which were perfectly complementary to HIF1 $\alpha$  or had no more than 4 mismatches to HIF1 $\alpha$ .

b. Table 1 of Exhibit A lists the ISIS # of each oligonucleotide targeted to HIF1 $\alpha$  and shows the sequence for each oligonucleotide. ISIS 330449 (SEQ ID NO: 446) was among the oligonucleotides designed in this study. In addition, twenty-three other oligonucleotides with a nucleotide sequence comprising at least 8 consecutive nucleobases of ISIS 330449 (SEQ ID NO: 446) were designed. These oligonucleotides are identified in Table 1 as ISIS #: 330447, 330448, 330450, 330451, 330452, 330453, 330454, 330455, 330456, 330457, 330458, 330459, 330460, 330461, 330462, 330463, 330464, 330465, 330466, 330467, 330468, 298698 and 326743.

5. In view of the foregoing evidence, prior to August 20, 2003, I conceived of and reduced to practice antisense oligonucleotides targeted to HIF1 $\alpha$  (SEQ ID NO: 133), including oligonucleotides comprising at least 8 consecutive nucleobases of SEQ ID NO: 446.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 9/13/06

By:   
Eric G. Marcusson, Ph.D.

## EXHIBIT A

*More HIF1/2x Crossreactors**I ordered more oligos to try to find one that cross-reacts well. I used the data from the first batch to identify areas that might work well.*

TABLE 1

ISIS #	Designer	Notebook	Page	Seq ID	Sequence	Matched Site	Matched Comments
330447	EMARCUS8	2362	25	247086	TCATG GTCACATGGA TGAGT	TRUE	0 HIF1 and 2 cross reactors
330448	EMARCUS8	2362	25	247087	CTCAT GGTCCACATGG ATGAG	TRUE	0 HIF1 and 2 cross reactors
330449	EMARCUS8	2362	25	247088	CCTCA TGGTCACATG GATGA	TRUE	0 HIF1 and 2 cross reactors
330450	EMARCUS8	2362	25	247089	TTGCT CATGGTCACA TGGAT	TRUE	0 HIF1 and 2 cross reactors
330451	EMARCUS8	2362	25	247090	TTTCC TCATGGTCAC ATGGA	TRUE	0 HIF1 and 2 cross reactors
330452	EMARCUS8	2362	25	247091	ATTTC CTCATGGTCA CATGG	TRUE	0 HIF1 and 2 cross reactors
330453	EMARCUS8	2362	25	247092	CATT CCTCATGGCT ACATG	TRUE	0 HIF1 and 2 cross reactors
330454	EMARCUS8	2362	25	247093	TGATT TCTCATGGT GACAT	TRUE	0 HIF1 and 2 cross reactors
330455	EMARCUS8	2362	25	247094	CTCAT TTCTCATGG TCACA	TRUE	0 HIF1 and 2 cross reactors
330456	EMARCUS8	2362	25	247095	TCTCA TTCTCATGG GTCAC	TRUE	0 HIF1 and 2 cross reactors
330457	EMARCUS8	2362	25	247096	CTCTC ATTCTCAT GGTCA	TRUE	0 HIF1 and 2 cross reactors
330458 Not Unique	EMARCUS8	2362	25	244487	TCTCT CATTTCTCA TGATC	TRUE	0 HIF1 and 2 cross reactors
330459	EMARCUS8	2362	25	247097	TCATG GTCACAGGA TGAGT	TRUE	0 HIF1 and 2 cross reactors
330460	EMARCUS8	2362	25	247098	CTCAT GGTCCAGGG ATGAG	TRUE	0 HIF1 and 2 cross reactors
330461	EMARCUS8	2362	25	247099	CCTCA TGGTCAGGG GATGA	TRUE	0 HIF1 and 2 cross reactors
330462 Not Unique	EMARCUS8	2362	25	248656	TCCTC ATGGTCGAG GATG	TRUE	0 HIF1 and 2 cross reactors
330463	EMARCUS8	2362	25	247100	CTCTC CATGGTCGA GGGAT	TRUE	0 HIF1 and 2 cross reactors
330464	EMARCUS8	2362	25	247101	TCTCC TCATGGTCG AGGGA	TRUE	0 HIF1 and 2 cross reactors
330465	EMARCUS8	2362	25	247102	ATGTC CTCATGGTC CAGGG	TRUE	0 HIF1 and 2 cross reactors
330466	EMARCUS8	2362	25	247103	AATCT CCTCATGGT GCGAG	TRUE	0 HIF1 and 2 cross reactors
330467	EMARCUS8	2362	25	247104	GAATC TCTCATGGT CCGAG	TRUE	0 HIF1 and 2 cross reactors
330468	EMARCUS8	2362	25	247105	ACGAA TCTCTCATG GTCGC	TRUE	0 HIF1 and 2 cross reactors
330469	EMARCUS8	2362	25	247106	CAGGA ATCTCTCAT GGTGG	TRUE	0 HIF1 and 2 cross reactors
330470	EMARCUS8	2362	25	247107	TGAGG AATCTCTCA TGGTC	TRUE	0 HIF1 and 2 cross reactors
				247108	CACGG CAATGAAGC CTCGA	TRUE	0 HIF1 and 2 cross reactors
				247109	AAGCC CTCGAAGGCT TTCA	TRUE	0 HIF1 and 2 cross reactors